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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,777	04/09/2004	Winston T.K. Cheng	MR2723-365	8832

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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,777	CHENG ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006 and 02 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,10,11,13 and 15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,10,11,13 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner in this application has changed. Please direct future correspondences to Examiner Michael C. Wilson, Art Unit 1632.

SEQ ID NO: 13 and 14 were nucleic acids in original sequence listing attached to the specification filed 4-9-04, which is now reflected in the sequence listing filed 11-2-06. SEQ ID NO: 15 was originally a 1448 bovine human fusion protein, which is now reflected in the sequence listing filed 11-2-06.

Claims 2-4, 7-9, 12 and 14 have been canceled. Claim 18 has been added. Claims 1, 5, 6, 10, 11, 13 and 15-18 are pending and under consideration.

Applicant's arguments filed 7-17-06 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The amendments to the specification have been entered. The sequence listing filed 7-17-06 was not entered. The sequence listing filed 11-2-06 was entered.

Claim Objections

The objections to claims 5, 6, 11, 12, 15 and 17 have been withdrawn in view of the amendment.

Claim 1 should refer to – a nucleotide sequence encoding ~~a~~ the B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15 -- to be clear.

All of the claims should be limited to a non-human transgenic mammal to more clearly reflect the species of mice, rats, goats, pigs, sheep and cows now in claim 1.

Claim 10 should clearly set forth that the light chain comprises the A3, C1 and C2 domains and that the heavy chain comprises the A1 and A2 domains. Use of parentheses is objectionable.

Double Patenting

The rejection of claim 1 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6-9 of copending Application No. 10/727,145 ('145) has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 101

The rejection of claims 1, 5, 6, 10, 11, 13 and 15-17 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

Enablement

The rejection of claims 1, 5, 6, 10, 11, 13 and 15-17 under 35 U.S.C. 112, first paragraph, enablement, has been withdrawn in view of the amendment.

Indefiniteness

Claims 1, 5, 6, 10, 11, 13, 15-17 remain rejected and claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear because it cannot be determined if SEQ ID NO: 15 is full length human FVIII that must have the B-domain deleted or if SEQ ID NO: 15 is B-domain deleted human FVIII. Clarification is required. It is noted that the phrase "B-domain deleted human clotting factor VIII" was known in the art at the time of filing (Soukharev, of record, pg 237, col. 2, line 6-13).

Claim 1 is unclear because the phrase "wherein an innate N-terminal 19-amino acid signal peptide is replaced by a mammary gland specific signal peptide sequence" is unclear. It is unclear to what the term "innate" refers. In particular, it cannot be determined if the "innate" signal peptide is amino acids 1-19 of SEQ ID NO: 15 that must be replaced or if the "innate" signal peptide refers to a signal peptide that has already been removed from SEQ ID NO: 15. Clarification is required.

Claim 5 is indefinite because it is unclear if the "signal peptide" refers to the "innate" signal peptide in (a) of claim 1 or the signal peptide in (b) of claim 1. Assuming the signal peptide of claim 5 is intended to further limit the signal peptide in (b) of claim 1, the phrase "a bovine α-lactalbumin signal peptide encoded by a DNA sequence of SEQ ID NO: 1" cannot further limit the bovine α-S1 lactalbumin peptide of SEQ ID NO: 13 in claim 1 because SEQ ID NO: 1 is a nucleic acid sequence while SEQ ID NO: 13 is an amino acid sequence. Applicants may use claim 5 to limit the bovine α-lactalbumin peptide of SEQ ID NO: 13 in claim 1 to the bovine α-lactalbumin peptide encoded by the nucleic acid sequence of SEQ ID NO: 1; however, claim 5 is not clear as written.

Claim 5 is indefinite because it is unclear if the restriction site is part of the downstream sequence of SEQ ID NO: 1 or if it is separate from SEQ ID NO: 1. If the

restriction sequence is separate from SEQ ID NO: 1, using claim 5 to limit only the signal peptide as written is a misnomer. Clarification is required.

Likewise, claim 6 is indefinite because it is unclear if the "signal peptide" refers to the "innate" signal peptide in (a) of claim 1 or the signal peptide in (b) of claim 1. Assuming the signal peptide of claim 6 is intended to further limit the signal peptide in (b) of claim 1, the phrase "a bovine α-S1 casein signal peptide encoded by a DNA sequence of SEQ ID NO: 2" cannot further limit the bovine α-S1 casein peptide of SEQ ID NO: 14 in claim 1 because SEQ ID NO: 2 is a nucleic acid sequence while SEQ ID NO: 14 is an amino acid sequence. Applicants may use claim 6 to limit the bovine α-S1 casein peptide of SEQ ID NO: 14 in claim 1 to the bovine α-S1 casein peptide encoded by the nucleic acid sequence of SEQ ID NO: 2; however, claim 6 is not clear as written.

Claim 6 is indefinite because it is unclear if the restriction site is part of the downstream sequence of SEQ ID NO: 2 or if it is separate from SEQ ID NO: 2. If the restriction sequence is separate from SEQ ID NO: 2, using claim 6 to limit only the signal peptide as written is a misnomer. Clarification is required.

Claim 10 is indefinite because "and the light chain...junction" is unclear. The phrase should begin "wherein the light chain..." to be clear.

Claim 11 is indefinite because it is dependent upon claim 9, which has been canceled.

Assuming claim 11 is dependent upon claim 1, claim 11 is indefinite because it does not appear to further limit claim 1. Claim 1 is already limited to using the bovine α-lactalbumin of SEQ ID NO: 13 or the bovine α-S1 casein peptide of SEQ ID NO: 14,

which are 19 and 15 amino acids in length, respectively. It cannot be determined how claim 11 would further limit claim 1.

Claim 13 does not make sense because a transgene is not introduced into "an embryo of the non-human transgenic animal" as claimed. Transgenes are introduced into embryos to make transgenics; transgenes are not introduced into embryos of transgenics as claimed.

Claim 13 does not make sense because transgenes do not have genomes as claimed. While the transgenic non-human animal may have a genome comprising a transgene, the transgene does not have a genome as claimed. The nucleotide sequences in claim 1 (a-c) should be introduced into an embryo in claim 13 step (i).

Claim 13, step ii) should be "the same species as the non-human transgenic animal" to be clear.

Claim 13, step iv, should be identifying the non-human transgenic animals of claim 1 to reflect the preamble of claim 13 and to be more clear.

Claim 15 is unclear because it is unclear how the expression cassette limitation further limits claim 13 or claim 1.

Claim 17 is indefinite because it is unclear how a purified hFVIII is "applicable to a supplementary therapy." It cannot be determined when a purified hFVIII is or is not applicable to therapy as claimed. The metes and bounds of when a therapy is "supplemental" cannot be determined.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 10, 13, and 17 under 35 U.S.C. 102(b) as being anticipated by Lubon (US Patent 6,255,554, Issued July 3, 2001) has been withdrawn. Lubon taught a non-human transgenic animal that expresses hFVIII protein in milk (claim 1 of Lubon) and a method of making said transgenic animal (claim 28). Lubon did not teach or suggest deleting the B-domain of the hFVIII. Therefore, Lubon did not teach a transgenic whose genome comprised a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15 as claimed (and described on pg 20, Example 2 of the specification).

The rejection of claims 1, 13 and 17 under 35 U.S.C. 102(b) as being anticipated by Paleyanda (Nature Biotechnology, 15:971-975, 1997) has been withdrawn. Paleyanda taught a transgenic pig that expresses full length hFVIII protein as a secretion product in milk and a method of making said transgenic pig. Paleyanda did not teach or suggest deleting the B-domain of the hFVIII. Thus, Paleyanda did not teach transgenic whose genome comprised a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15 as claimed (and described on pg 20, Example 2 of the specification).

The rejection of claims 1, 5, 11, 13, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen (Transgenic Research, 11:257-268, 2002) has been withdrawn. Chen taught a transgenic mouse that expresses full length hFVIII protein operably linked to the α-LA promoter as a secretion product in milk and a method of making said transgenic mouse. Chen did not teach or suggest deleting the B-domain of the hFVIII. Thus, Chen did not teach transgenic whose genome comprised

a nucleotide sequence encoding a B-domain deleted human clotting factor VIII (FVIII) polypeptide of SEQ ID NO: 15 as claimed (and described on pg 20, Example 2 of the specification).

The provisional rejection of claim 1 under 35 U.S.C. 102(e) as being anticipated by copending Application No. 10/727,145 ('145) which has a common inventor with the instant application has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

In view of the amendments, the previous rejection has been withdrawn in favor of the following two obvious rejections:

Claims 1, 5, 10, 11, 13, 15 and 17 remain rejected and claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Transgenic Research, 11:257-268, 2002) in view of Soukharev (Blood Cells, Molecules and Diseases, 28:234-248, 2002) and supported by Lubon (US Patent 6,255,554, Issued July 3, 2001).

Chen made a transgenic mouse comprising a vector encoding 7.2 kb of hFVIII coding region operably linked to the 2.0 kb bovine α-LA promoter and 19 amino acid bovine α-LA signal peptide sequence (pg 258, col. 2, first full paragraph; paragraph bridging pg 258-259). The 19 amino acid leader sequence of Chen is the 19 amino acid signal peptide of SEQ ID NO: 13 and encoded by SEQ ID NO: 1. The mouse was made by introducing the transgene construct (i.e. expression cassette) into an embryo, implanting the embryo into a recipient female, allowing the embryo to develop to term, and testing the resulting offspring and identifying mice that secreted hFVIII in milk

(paragraph bridging columns 1 and 2 of pg 263). Chen did not delete the B-domain of hFVIII.

However, Soukharev suggested making transgenic mammals expressing B-domain deleted FVIII to improve yield of FVIII (pg 241, paragraph bridging columns 1 and 2). "[A]nother approach to improve recombinant FVIII molecule is to introduce modifications to improve its effective secretion from FVIII-expressing cell" (page 239, col. 1, paragraph 1, lines 1-4) and that "removal of the B domain...was found to dramatically improve the yield of FVIII" (page 237, col. 2, lines 3-6). Soukharev taught "an attractive possibility to increase the yield of rFVIII is to produce a biologically active form of FVIII by coexpressing its heavy and light chains" (page 239, paragraph 2, line 1 to col. 2, line 2). The phrase "a B-domain deleted hFVIII polypeptide of SEQ ID NO: 15" encompasses any B-domain deleted hFVIII protein of SEQ ID NO: 15. The nucleic acid sequence encoding the B-domain deleted hFVIII taught by Soukharev encodes "a B-domain deleted hFVIII polypeptide of SEQ ID NO: 15" as in claim 1. Without evidence to the contrary, the B-domain deleted hFVIII taught by Soukharev inherently produces a hFVIII comprising a light chain (A3-C1-C2 domain) and a heavy chain (A1-A2 domain) operably linked by a junction as in claim 10.

Thus, it was obvious to make a transgenic mouse encoding hFVIII as taught by Chen, wherein the hFVIII had a deletion in the B-domain as taught by Soukharev. Soukharev provides motivation on pg 241, lines 1-5. Those of skill would have a reasonable expectation of successfully improving the yield of hFVIII because results in

vitro improved the yield (pg 237, "Genetic engineering to improve the yield of recombinant FVIII).

Lubon provides further evidence that fragments of hFVIII could be made in a non-human transgenic animal (claim 1 of Lubon).

Claim 5 is included because of the indefiniteness of the claim and because the vector used to make the transgenic inherently has a restriction enzyme cloning site somewhere downstream of SEQ ID NO: 1.

Claim 11 is included because it is currently dependent upon claim 9, which has been canceled, and does not further limit claim 1.

Claim 17 is included because the hFVIII produced is able to treat patients.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 5, 6, 10, 11, 13, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Transgenic Research, 11:257-268, 2002) in view of Soukharev (Blood Cells, Molecules and Diseases, 28:234-248, 2002) and supported by Lubon (US Patent 6,255,554, Issued July 3, 2001) as applied to claims 1, 5, 10, 11, 13, 15, 17 and 18 above, and further in view of DeBoer (US Patent 5,633,076, Issued May 27, 1997).

The combined teachings of Chen and Soukharev taught making a transgenic mouse comprising a vector encoding B-domain deleted hFVIII coding region operably linked to the 2.0 kb bovine α-LA promoter and 19 amino acid signal peptide sequence

(Chen - pg 258, col. 2, first full paragraph; paragraph bridging pg 258-259; Soukharev - pg 241, paragraph bridging columns 1 and 2; page 239, col. 1, paragraph 1, lines 1-4; page 237, col. 2, lines 3-6; page 239, paragraph 2, line 1 to col. 2, line 2; see 103 rejection above). The 19 amino acid leader sequence of Chen is the 19 amino acid signal peptide of SEQ ID NO: 13. The mouse secreted hFVIII in milk (paragraph bridging columns 1 and 2 of pg 263). The combined teachings of Chen and Soukharev did not teach replacing the 19 amino acid α-LA signal peptide of SEQ ID NO: 13 with the 15 amino acid α-SI casein signal peptide of SEQ ID NO: 14.

However, DeBoer taught a nucleic acid construct comprising various nucleic acid elements for the optimization of producing recombinant protein in the milk of transgenic animals, said recombinant protein including FVIII (col. 7, line 12) including the alpha S1 casein secretion signal peptide (col. 7, lines 18-27). DeBoer also taught using the alpha-lactalbumin, whey acidic protein, beta-casein and alpha S1 casein (col. 2, line 53 to col. 3, line 5).

Thus, it was obvious to make a transgenic mouse encoding B-domain deleted hFVIII operably linked to the as taught by the combined teachings of Chen and Soukharev, wherein the a-lactalbumin signal peptide of SEQ ID NO: 13 was replaced with the α-S1 casein signal peptide of SEQ ID NO: 14. One of ordinary skill in the art would have been motivated to use the α-S1 casein signal peptide instead of the α-lactalbumin signal peptide to increase secretion of hFVIII into the milk. Those of skill would have a reasonable expectation of successfully swapping signal peptides in view of the teachings of DeBoer.

Lubon provides further evidence that signal peptides could be readily swapped to increase secretion into the milk of a non-human transgenic animal. Lubon states the "[i]mportant to the present invention are regulatory sequences that direct secretion of proteins into milk and/or other body fluids of the transgenic animal. In this regard, both homologous and heterologous regulatory sequences are useful in the invention. Generally, regulatory sequences known to direct the secretion of milk proteins, such as either signal peptides from milk proteins or the nascent target polypeptide, can be used..." (col. 6, lines 45-52).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER